

FORM PTO-1390  
(REV 10-95)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. §371**

MERCK 2384

U.S. APPLICATION NO. (If known, see 37 CFR §1.5)

**10/069054**

INTERNATIONAL APPLICATION NO.

PCT/EP00/07664

INTERNATIONAL FILING DATE

8 AUGUST 2000

PRIORITY DATE CLAIMED

21 AUGUST 1999

TITLE OF INVENTION

PIPERIDINE ALCOHOLS

APPLICANT(S) FOR DO/EO/US


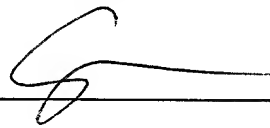
PRUECHER, Helmut, et al

**Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:**

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19<sup>th</sup> month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

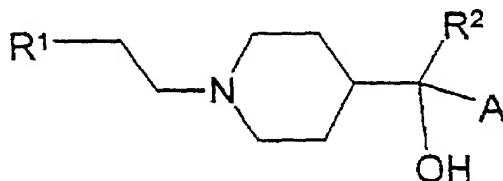
**Items 11. to 16. below concern document(s) or information included:**

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ☐ A **FIRST** preliminary amendment.
- ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR §1.5) <b>10/069054</b>		INTERNATIONAL APPLICATION NO. PCT/EP00/07664		ATTORNEY'S DOCKET NUMBER MERCK 2384	
17. <input checked="" type="checkbox"/> The following fees are submitted:  <b>BASIC NATIONAL FEE ( 37 CFR §1.492 (a) (1) - (5)):</b>  Search Report has been prepared by the EPO or JPO..... \$890.00 International preliminary examination fee paid to USPTO (37 CFR §1.482)..... \$710.00 No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))..... \$740.00 Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO..... \$1040.00 International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... \$100.00  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>CALCULATIONS</b> PTO USE ONLY	
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 C.F.R. §1.492(e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30					
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	8 - 20 =	0	x \$ 18.00	\$0.00	
Independent claims	1 - 3 =	0	x \$ 84.00	\$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$ 280.00		
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$890.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be					
<b>SUBTOTAL =</b>				\$890.00	
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 C.F.R. §1.492(f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30					
<b>TOTAL NATIONAL FEE =</b>				\$890.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). \$40.00 per property.					
<b>TOTAL FEES ENCLOSED =</b>				\$890.00	
				Amount to be refunded:	
				charged:	
a. <input checked="" type="checkbox"/> A check in the amount of <u>\$890.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>13-3402</u> in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>13-3402</u> . A duplicate copy of this sheet is enclosed.					
<b>NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>					
SEND ALL CORRESPONDENCE TO: Customer Number 23,599					
 <b>23599</b> PATENT TRADEMARK OFFICE			SIGNATURE  <b>Anthony J. Zelano</b> NAME <u>27,969</u> REGISTRATION NUMBER		
Filed: 21 FEBRUARY 2002 AJZ:kmo					

## Piperidine alcohols

The invention relates to compounds of the formula I



I

5

in which

- 10  $R^1, R^2$  in each case independently of one another are aryl or Het,  
 aryl is phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, CN, A, OA or OH,  
 Het is a mono- or binuclear unsaturated heterocyclic ring system which is unsubstituted  
 15 or mono-, di- or trisubstituted by Hal, CN, A, OA or OH and which contains one, two or three identical or different heteroatoms such as nitrogen, oxygen and sulfur,  
 A is alkyl having 1-6 C atoms,  
 20 Hal is F, Cl, Br or I,

and their physiologically acceptable salts and solvates.

- 25 The invention was based on the object of finding novel compounds having valuable properties, in particular those which can be used for the production of medicaments.

- 30 It has been found that the compounds of the formula I and their physiologically acceptable salts and solvates have valuable pharmacological properties together with good tolerability, as they have actions on the central nervous system. The compounds have a strong affinity

for 5-HT<sub>2A</sub> receptors; they furthermore exhibit 5-HT<sub>2A</sub> receptor-antagonistic properties.

Other compounds which also show 5-HT<sub>2A</sub>-antagonistic actions are described, for example, in EP 0320983 or in WO 99/11641. 1-Phenylethyl-4-piperidinemethanol derivatives are described in EP 0208235 and in EP 0531410.

- 10 For the in-vitro detection of the affinity for 5-HT<sub>2A</sub> receptors, it is possible to use, for example, the following test (Example A1). The 5-HT<sub>2A</sub> receptors are exposed to both [<sup>3</sup>H]ketanserin (a substance known for its affinity for the receptor) and the test compound.
- 15 The decrease in the binding of [<sup>3</sup>H]ketanserin to the receptor is a sign of the affinity of the test substance for the 5-HT<sub>2A</sub> receptor. Detection is carried out analogously to the description of J.E. Leysen et al., Molecular Pharmacology, 1982, 21: 301-314 or as
- 20 also described, for example, in EP 0320983.

The experimental proof that the compounds according to the invention have affinity for the 5-HT<sub>2A</sub> receptor is demonstrated experimentally in vitro, as described

25 above, for some representative compounds of the formula I. The pharmacological test data are summarized in Example A1, Table A. As a comparison, the compound (+)- $\alpha$ -(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)-ethyl]-4-piperidinemethanol, which is disclosed in

30 EP 0531410, is additionally listed.

The efficacy of the compounds according to the invention as 5-HT<sub>2A</sub> receptor antagonists can be measured in vitro analogously to W. Feniuk et al., Mechanisms of

35 5-hydroxytryptamine-induced vasoconstriction, in: The Peripheral Actions of 5-Hydroxytryptamine, ed. Fozard JR, Oxford University Press, New York, 1989, p. 110. Thus the contractility of the rat tail artery, caused by 5-hydroxytryptamine, is mediated by 5-HT<sub>2A</sub> receptors.

For the test system, vessel rings, prepared from the ventral rat tail artery, are subjected to perfusion with an oxygen-saturated solution in an organ bath. By introduction of increasing concentrations of 5-hydroxy-tryptamine into the solution, a response to the cumulative concentration of 5-HT is obtained. The test compound is then added to the organ bath in suitable concentrations and a second concentration curve is measured for 5-HT. The strength of the test compound on the shift of the 5-HT-induced concentration curve to higher 5-HT concentrations is a measure of the 5-HT<sub>2A</sub> receptor-antagonistic property in vitro.

The 5-HT<sub>2A</sub>-antagonistic property can be determined in vivo analogously to M.D. Serdar et al., Psychopharmacology, 1996, 128: 198-205.

Serotonin-2(5-HT<sub>2</sub>)agonists such as 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) induce stereotypic behaviour patterns such as, for example, head-twitching or ear-scratching in various animals such as, for example, mice or rats (N.A. Darmani et al., Pharmacol. Biochem. Behav. 1989, 36: 901-906; N.A. Darmani et al., Pharmacol. Biochem. Behav. 1990, 37: 95-99; N.A. Darmani et al., Pharmacol. Biochem. Behav. 1994, 48: 383-396; D.L. Willins and H.Y. Meltzer, J. Pharmacol. Exp. Ther., 1997, 282: 699-706). The response of head-twitching is selectively prevented by 5-HT<sub>2A</sub> antagonists, however ear-scratching is sensitive to 5-HT<sub>2C</sub> antagonists (N.A. Darmani et al., Pharmacol. Biochem. Behav. 1990, 37: 95-99; N.A. Darmani and C.F. Gerdes, Pharmacol. Biochem. Behav. 1995, 50: 545-550; D.L. Willins and H.Y. Meltzer, J. Pharmacol. Exp. Ther., 1997, 282: 699-706).

DOI-induced head-twitching in mice is used in order to test compounds having 5-HT<sub>2A</sub> antagonistic properties. The test compound is orally administered to male mice. 30 minutes later, 3 mg/kg of DOI is [sic] are

administered intraperitoneally. The animals are observed for 15 minutes and the number of head twitches is noted. Quantification of the in vivo antagonistic effect of the test compounds ensues by comparison with  
5 the number of head twitches from those investigations in which the animals were only DOI-treated.

Surprisingly, the compounds according to the invention have, in comparison to the prior art, an improved  
10 suppression of the behaviour elicited on oral administration. The pharmacological test data are summarized in Example A2 in Table B. As a comparison, the compound (+)- $\alpha$ -(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol, which is  
15 disclosed in EP 0531410, is additionally listed.

The test results indicate an unexpectedly improved bioavailability of the compounds according to the invention in comparison to the prior art.

20 The compounds of the formula I are therefore suitable both in veterinary and in human medicine for the treatment of functional disorders of the central nervous system and also of inflammation. They can be  
25 used for the prophylaxis and for the control of the sequelae of cerebral infarcts (cerebral apoplexy) such as stroke and cerebral ischaemias and for the treatment of extrapyramidal motor side effects of neuroleptics and also of Parkinson's disease, for the acute and  
30 symptomatic therapy of Alzheimer's disease and the treatment of amyotrophic lateral sclerosis. They are likewise suitable as therapeutics for the treatment of brain and spinal cord traumata. In particular, however, they are suitable as pharmaceutical active compounds  
35 for anxiolytics, antidepressants, antipsychotics, neuroleptics, antihypertensives and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD), anxiety states, panic attacks, psychoses, schizophrenia, anorexia, delusional

obsessions, agoraphobia, migraine, Alzheimer's disease, sleep disorders, tardive dyskinesias, learning disorders, age-dependent memory disorders, eating disorders such as bulimia, drug abuse and/or sexual functional disorders.

In addition, they are suitable for the treatment of endocrine disorders such as hyperprolactinaemia, furthermore in vasospasms, hypertension and gastrointestinal disorders.

They are furthermore suitable for the treatment of cardiovascular disorders and also extrapyramidal symptoms as described in WO 99/11641 on page 2, lines 24-30.

The compounds according to the invention are further suitable for decreasing intraocular pressure and for the treatment of glaucoma. They are also suitable in animals for the prophylaxis and treatment of symptoms of intoxication on the administration of ergovaline.

The compounds are furthermore suitable for the treatment of disorders of the cardiovascular system (WO 99/11641, page 3, lines 14-15).

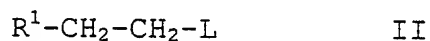
The compounds according to the invention can also be employed together with other active compounds in the treatment of schizophrenia. Possible other active compounds are the compounds mentioned in WO 99/11641 on page 13, lines 20-26.

They can furthermore be employed as intermediates for the production of further pharmaceutical active compounds.

The invention relates to the piperidine alcohols of the formula I and to their physiologically acceptable acid addition salts. The invention also relates to the solvates, e.g. hydrates or alcoholates, of these compounds.

The invention accordingly relates to the compounds of the formula I and a process for the preparation of compounds of the formula I according to Claim 1.

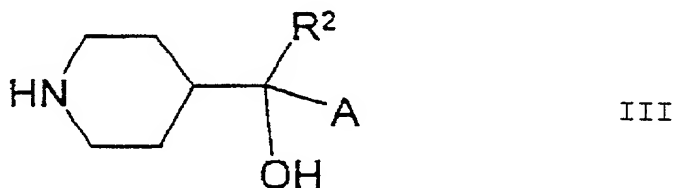
- 5 The process for the preparation of compounds of the formula I according to Claim 1 is characterized in that  
a) a compound of the formula II



10

in which L is Cl, Br, I or a free or reactively [sic] functionally modified OH group,  
and  $R^1$  has the meaning indicated in Claim 1,  
is reacted with a compound of the formula III

15

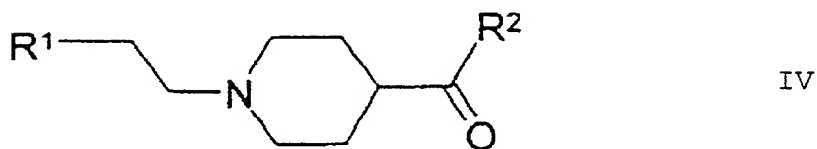


in which  $R^2$  and A have the meanings indicated in Claim 1,

20

or

- b) a compound of the formula IV



25

in which  $R^1$  and  $R^2$  have the meanings indicated in Claim 1,

is reacted with a compound of the formula V

30





in which R is iodine or bromine, X is Mg  
and A has the meaning indicated in Claim 1,  
in a Grignard reaction,

5 or

c) it is liberated from one of its functional  
derivatives by treating with a solvolysing or  
hydrogenolysing agent,

10

or

15

d) a base of the formula I which is obtained is  
converted into one of its salts by treating with an  
acid.

20

The invention also relates to the compounds of the  
formula I according to Claim 1, and to their  
physiologically acceptable salts and solvates as  
medicaments.

25

The invention relates in particular to the compounds of  
the formula I according to Claim 1, and also their  
physiologically acceptable salts and solvates as  
medicaments having 5-HT<sub>2A</sub> receptor-antagonistic action.

The invention also relates to the compounds of the  
formula I, and their enantiomers and their salts.

30

For all radicals which occur a number of times, such  
as, for example, A or Hal, it holds true that their  
meanings are independent of one another.

35

The radical A is alkyl and has 1 to 6, preferably 1, 2,  
3 or 4, in particular 1 or 2, C atoms. Alkyl is  
therefore in particular, for example, methyl,  
furthermore ethyl, n-propyl, isopropyl, n-butyl, sec-  
butyl or tert-butyl, furthermore also pentyl, 1-, 2- or  
3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl,

1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl. A  
5 furthermore denotes completely or partially fluorinated or chlorinated alkyl radicals, such as, for example, trifluoromethyl or pentafluoroethyl.

A is very particularly preferably methyl, ethyl, propyl, isopropyl or butyl.

10

OA is preferably methoxy, furthermore also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy.

15

Hal is fluorine, chlorine, bromine or iodine, in particular fluorine or chlorine.

Aryl is unsubstituted, preferably - as indicated - monosubstituted phenyl, specifically preferably phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-trifluoromethoxyphenyl, o-, m- or p-cyanophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-difluoromethoxyphenyl, o-, m- or p-fluoromethoxyphenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or  
20 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2-chloro-3-methyl-, 2-chloro-4-methyl-, 2-chloro-5-methyl-, 2-chloro-6-methyl-, 2-methyl-3-chloro-, 2-methyl-4-chloro-, 2-methyl-  
25 5-chloro-, 2-methyl-6-chloro-, 3-chloro-4-methyl-, 3-chloro-5-methyl- or 3-methyl-4-chlorophenyl, 2-bromo-3-methyl-, 2-bromo-4-methyl-, 2-bromo-5-methyl-, 2-bromo-6-methyl-, 2-methyl-3-bromo-, 2-methyl-4-bromo-, 2-methyl-5-bromo-, 2-methyl-6-bromo-,

30

35

3-bromo-4-methyl-, 3-bromo-5-methyl- or 3-methyl-4-bromophenyl, 2,5- or 3,4-dimethoxyphenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-tri-tert-butylphenyl, furthermore preferably 3,5-ditri-  
5 fluoromethylphenyl, 2,5-dimethylphenyl, 2-hydroxy-3,5-dichlorophenyl, 2-fluoro-5- or 4-fluoro-3-trifluoromethylphenyl, 4-chloro-2- or 4-chloro-3-trifluoromethyl-, 2-chloro-4- or 2-chloro-5-trifluoromethylphenyl, 4-bromo-2- or 4-bromo-3-trifluoromethyl-  
10 phenyl, p-iodophenyl, 2,5-dimethoxy-4-nitrophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3,5-dimethylphenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 2,4-dichloro-5-methylphenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 2-methoxy-5-methylphenyl or  
15 2,4,6-triisopropylphenyl.

Het is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2 [sic] or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or  
20 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl,  
25 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4-H-thiopyranyl [sic], 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-,  
30 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, benzo[1,3]dioxol-4- or -5-yl, benzo[1,4]dioxan-5- or -6-yl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-,  
35 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl,

3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl.

Het is very particularly preferably 2- or 3-furyl, 2- or 3-thienyl, 4- or 5-thiazolyl, 4-pyridyl which is mono- or disubstituted by Hal or A.

R<sup>1</sup> is particularly preferably, for example, 2,3-dimethoxyphenyl, 2-, 3- or 4-fluorophenyl, 2,4-dichlorophenyl, 2,3- 2,4-, 3,4- or 2,6-difluorophenyl, 2- or 4-trifluoromethylphenyl, 2-, 3- or 4-tolyl, 2-chloro-6-fluorophenyl, 2-fluoro-4-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, 4-fluoro-6-trifluoromethylphenyl, 3-fluoro-4-trifluoromethylphenyl, 2-fluoro-6-trifluoromethylphenyl, 4-cyanophenyl, thiophen-2- or 3-yl [sic], 5-chlorothiophen-2-yl, 5-methylthiophen-2-yl, 2,5-dichlorothiophen-3-yl, 2-chloro-3-methylthiophen-5-yl, bromothiophen-5-yl, 2-chloro-5-methylthiophen-4-yl, 2-methoxythiophen-5-yl, 2- or 4-methylthiazol-4- or -5-yl, and pyridin-4-yl.

R<sup>2</sup> is very particularly preferably phenyl, 4-chlorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 4-trifluoromethylphenyl, thiophen-2-yl, 5-chlorothiophen-2-yl, 2,5-dichlorothiophen-3-yl or benzodioxan-5- or 6-yl [sic].

Accordingly, the invention relates in particular to those compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following subformulae Ia to Ig, which correspond to the formula I and in which the radicals not designated in greater detail have the meaning indicated in the formula I, but in which

in Ia R<sup>1</sup> is Het;

- in Ib     $R^1$     is Het,  
          $R^2$     is aryl;
- 5    in Ic     $R^1$     is is [sic] Het or aryl,  
          $R^2$     is is [sic] aryl,  
         Het    is is [sic] a mono- or binuclear  
                 unsaturated heterocyclic ring system  
10                   which is unsubstituted or mono- or  
                 disubstituted by Hal, OA or A and which  
                 contains one or two identical or  
                 different heteroatoms such as nitrogen,  
                 oxygen and sulfur;
- 15    in Id     $R^1$     is Het or aryl,  
          $R^2$     is aryl,  
         Het    is a mono- or binuclear unsaturated  
                 heterocyclic ring system which is  
20                   unsubstituted or mono- or disubstituted  
                 by Hal, OA or A and which contains one  
                 or two identical or different hetero-  
                 atoms such as nitrogen, oxygen and  
                 sulfur,  
                 aryl    is phenyl which is unsubstituted or  
25                   mono-, di- or trisubstituted by Hal, A,  
                 CN, OA or OH;
- in Ie     $R^1$     is Het or aryl,  
          $R^2$     is Het or aryl,  
30           Het    is thienyl, thiazolyl, pyridyl or  
                 benzo[1,4]dioxanyl, which is  
                 unsubstituted or mono- or disubstituted  
                 by Hal, OA or A,  
                 aryl    is phenyl which is unsubstituted or  
35                   mono-, di- or trisubstituted by Hal, A,  
                 CN, OA or OH;
- in If     $R^1$     is Het or aryl,  
          $R^2$     is aryl,

Het is thienyl, thiazolyl or benzo[1,4]-  
dioxanyl, which is unsubstituted or  
mono- or disubstituted by Hal, OA or A,  
aryl is phenyl which is unsubstituted or  
mono-, di- or trisubstituted by Hal or  
CF<sub>3</sub>;

in Ig R<sup>1</sup> is Het,  
R<sup>2</sup> is aryl,

Het is thienyl, thiazolyl or benzo[1,4]-  
dioxanyl, which is unsubstituted or  
mono- or disubstituted by Hal, OA or A,  
aryl is phenyl which is unsubstituted or  
mono-, di- or trisubstituted by Hal or  
CF<sub>3</sub>.

The compounds of the formula I and also the starting  
substances for their preparation are otherwise prepared  
by methods known per se, such as are described in the  
literature (e.g. in the standard works such as Houben-  
Weyl, Methoden der Organischen Chemie [Methods of  
Organic Chemistry], Georg Thieme Verlag, Stuttgart;  
Organic Reactions, John Wiley & Sons, Inc., New York),  
namely under reaction conditions such as are known and  
suitable for the reactions mentioned. Use can also be  
made in this case of variants which are known per se,  
but not mentioned here in greater detail.

If desired, the starting substances for the claimed  
process can also be formed in situ in such a way that  
they are not isolated from the reaction mixture, but  
immediately reacted further to give the compounds of  
the formula I. On the other hand, it is possible to  
carry out the reaction stepwise.

In the compounds of the formula II, the radical L is  
preferably Cl or Br; however, it can also be I, OH or  
otherwise preferably a reactively [sic] functionally  
modified OH group, in particular alkylsulfonyloxy

having 1-6 (e.g. methanesulfonyloxy) or arylsulfonyloxy  
having 6-10 C atoms (e.g. benzenesulfonyloxy, p-  
toluenesulfonyloxy, 1- or 2-naphthalenesulfonyloxy) or  
otherwise trichloromethoxy, alkoxy, such as, for  
5 example, methoxy, ethoxy, propoxy or butoxy, further-  
more also phenoxy.

The compounds of the formula I can preferably be  
obtained by reacting compounds of the formula II with  
10 compounds of the formula III.

As a rule, the starting substances of the formulae II  
and III are known; the unknown compounds of the  
formulae II and III can easily be prepared analogously  
15 to the known compounds.

The reaction of the compounds II and III proceeds  
according to methods such as are known from the  
literature for the alkylation or acylation of amines.  
20 However, it is also possible to react the compounds in  
the presence of an indifferent solvent. Suitable  
solvents are, for example, hydrocarbons, such as  
benzene, toluene, xylene; ketones such as acetone,  
butanone; alcohols such as methanol, ethanol,  
25 isopropanol, N-butanol [sic]; ethers such as  
tetrahydrofuran (THF) or dioxane; amides such as  
dimethylformamide (DMF) or N-methylpyrrolidone;  
nitriles such as acetonitrile, and, if appropriate,  
also mixtures of these solvents with one another or  
30 mixtures with water. The addition of an acid-binding  
agent, for example of an alkali metal or alkaline earth  
metal hydroxide, carbonate or bicarbonate or of another  
salt of a weak acid of the alkali or alkaline earth  
metals, preferably of potassium, sodium or calcium, or  
35 the addition of an organic base such as triethylamine,  
dimethylaniline, pyridine or quinoline or of an excess  
of piperidine derivative of the formula II can be  
favourable. Depending on the conditions used, the  
reaction time is between a few minutes and 14 days; the

reaction temperature is between approximately 0 and 150°, normally between 20 and 130°.

5 The compounds of the formula I can also be obtained by reacting compounds of the formula IV with compounds of the formula V.

10 As a rule, the starting substances of the formulae IV and V are known; the unknown compounds of the formulae IV and V can easily be prepared analogously to the known compounds.

15 The reaction of the compounds IV and V proceeds according to methods such as are known from the literature for the Grignard reaction.

20 The compounds of the formulae [sic] I can furthermore be obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis.

25 Preferred starting substances for the solvolysis or hydrogenolysis are those which, instead of one or more free hydroxyl groups, contain corresponding protected hydroxyl groups.

30 These are preferably compounds which, instead of the H atom of a hydroxyl group, carry a hydroxyl protective group, e.g. those which correspond to the formula I, but instead of a hydroxyl group contain an R''O-phenyl group (in which R'' is a hydroxyl protective group).

35 The expression "hydroxyl protective group" is generally known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other positions in the molecule. Typical groups of this type are, in particular, unsubstituted or substituted acyl-, aryl-, aralkoxymethyl- or aralkyl groups. The



expression "acyl group" is to be interpreted in the widest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, in particular alkoxycarbonyl, aryloxy carbonyl and especially aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl such as acetyl, propionyl, butyryl; aralkanoyl such as phenylacetyl; aroyl such as benzoyl or toluylyl; aryloxyalkanoyl such as POA; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC, 2-iodoethoxycarbonyl; aralkyloxy carbonyl such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxy carbonyl.

The nature and size of the hydroxyl protective groups is not critical, as they are removed again after the desired chemical reaction or reaction sequence; groups having 1-20, in particular 1-10, C atoms are preferred. Examples of hydroxyl protective groups are, inter alia, benzyl, p-nitrobenzoyl [sic], p-toluenesulfonyl, tert-butyl and acetyl, benzyl and tert-butyl being particularly preferred.

The liberation of the compounds of the formula I from their functional derivatives is carried out - depending on the protective group used - e.g. using strong acids, expediently using TFA or perchloric acid, but also using other strong inorganic acids such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids such as trichloroacetic acid or sulfonic acids such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but not always necessary. Suitable inert solvents are preferably organic solvents, for example carboxylic acids such as acetic acid, ethers such as tetrahydrofuran or dioxane, amides such as DMF, halogenated hydrocarbons such as dichloromethane, in addition also alcohols such as methanol, ethanol or isopropanol, and also water. In addition, mixtures of the abovementioned solvents are

suitable. TFA is preferably used in an excess without addition of a further solvent, perchloric acid in the form of a mixture of acetic acid and 70% strength perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are expediently between approximately 0 and approximately 50°; the reaction is preferably carried out at between 15 and 30° (room temperature).

Hydrogenolytically removable protective groups (e.g. CBZ or benzyl) can be removed, for example, by treating with hydrogen in the presence of a catalyst (e.g. of a noble metal catalyst such as palladium, expediently on a support such as carbon). Suitable solvents in this case are those indicated above, in particular, for example, alcohols such as methanol or ethanol or amides such as DMF. As a rule, the hydrogenolysis is carried out at temperatures between approximately 0 and 100° and pressures between approximately 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group takes place, for example, readily on 5 to 10% Pd/C in methanol or, using ammonium formate (instead of hydrogen), on Pd/C in methanol/DMF at 20-30°.

As a rule, the respective components are known or can be prepared by known processes as already described.

A base of the formula I obtained can be converted into the associated acid addition salt using an acid. For this reaction, suitable acids are those which yield physiologically acceptable salts. Thus inorganic acids can be used, e.g. sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid, sulfamic acid, furthermore organic acids, specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, such as formic acid, acetic acid,

propionic acid, pivalic acid, diethylacetic acid,  
malonic acid, succinic acid, pimelic acid, fumaric  
acid, maleic acid, lactic acid, tartaric acid, malic  
acid, benzoic acid, salicylic acid, 2-phenylpropionic  
5 acid, citric acid, gluconic acid, ascorbic acid,  
nicotinic acid, isonicotinic acid, methane- or  
ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxy-  
ethanesulfonic acid, benzenesulfonic acid, p-toluene-  
sulfonic acid, naphthalenemono- and -disulfonic acids  
10 and laurylsulfuric acid.

The free bases of the formula I can, if desired, be  
liberated from their salts by treatment with strong  
bases such as sodium or potassium hydroxide, or sodium  
15 or potassium carbonate, if no further acidic groups are  
present in the molecule. In those cases where the  
compounds of the formula I have acidic groups, such as,  
for example, phenolic OH, salt formation can likewise  
be achieved by treatment with bases. Suitable bases are  
20 alkali metal hydroxides, alkaline earth metal  
hydroxides or organic bases in the form of primary,  
secondary or tertiary amines.

On account of their molecular structure, compounds of  
25 the formula I according to the invention can be chiral  
and can accordingly occur in two enantiomeric forms.  
They can therefore be present in racemic or in  
optically active form.

30 As the pharmaceutical activity of the racemates or the  
stereoisomers of the compounds according to the  
invention can differ, it may be desirable to use the  
enantiomers. In these cases, the final product or else  
even the intermediates can be resolved into  
35 enantiomeric compounds by chemical or physical measures  
known to the person skilled in the art or even employed  
as such in the synthesis.

- In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Suitable resolving agents are, for example, optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitably N-protected amino acids (e.g. N-benzoylproline or N-benzenesulfonylproline) or the various optically active camphorsulfonic acids.
- Chromatographic separation of enantiomers with the aid of an optically active resolving agent (e.g. dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatized methacrylate polymers attached to silica gel) is also advantageous. Suitable eluents for this are aqueous or alcoholic solvent mixtures such as, for example, hexane/isopropanol/acetonitrile, e.g. in the ratio 82:15:3.
- Under particular conditions, however, it is also possible even during the synthesis to employ corresponding enantiomerically pure intermediates which have been prepared by one of the abovementioned processes. In this case, the chirality is retained in the course of the further synthesis.
- Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.
- The invention furthermore relates to the medicaments according to the invention having 5-HT<sub>2A</sub> receptor-antagonistic action for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, anorexia nervosa, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

The invention also relates to a pharmaceutical preparation comprising at least one medicament according to the invention and also, if appropriate, vehicles and/or excipients and, if appropriate, other active compounds.

In this case, the medicaments can be brought into a suitable dose form together with at least one solid, liquid and/or semiliquid vehicle or excipient and, if appropriate, in combination with one or more further active compound(s).

The invention furthermore relates to the use of the compounds according to the invention and/or of their physiologically acceptable salts and solvates for the production of a medicament having 5-HT<sub>2A</sub> receptor-antagonistic action.

The invention also relates to the use of the compounds according to the invention and/or of their physiologically acceptable salts and solvates for the production of a medicament having 5-HT<sub>2A</sub> receptor-antagonistic action for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, anorexia nervosa, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

The pharmaceutical preparations can be employed as medicaments in human and veterinary medicine. Suitable vehicles are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium

stearate, talc and petroleum jelly. In particular, tablets, coated tablets, capsules, syrups, suspensions, drops or suppositories are used for enteral administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilizates obtained can be used, for example, for the production of injection preparations.

The preparations indicated can be sterilized and/or can contain excipients such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or aromatic substances. They can, if desired, also contain one or more further active compounds, e.g. one or more vitamins.

In this case, the substances according to the invention are as a rule administered in analogy to known preparations, preferably in doses between approximately 0.1 and 500 mg, in particular between 5 and 300 mg, per dose unit. The daily dose is preferably between approximately 0.01 and 250 mg/kg, in particular between 0.02 and 100 mg/kg, of body weight.

The specific dose for each intended patient depends, however, on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, on the excretion rate, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

Above and below, all temperatures are indicated in °C. In the examples below, "customary working up" means: if

necessary, the solvent is removed, if necessary, water is added, if necessary, the mixture is adjusted, depending on the constitution of the final product, to a pH of between 2 and 10 and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate, filtered and concentrated, and the residue is purified by chromatography on silica gel and/or by crystallization.

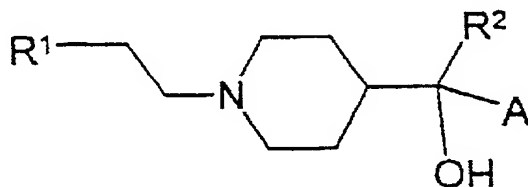
10 Example A1

Preparation of a suspension of 5-HT<sub>2A</sub> receptors:  
Frontal rat cortex is homogenized in ice-cold buffer. The homogenate is centrifuged for 10 minutes at 4°C and 50,000 × [sic]. The pellet is resuspended in 2.5 ml of ice-cold tris buffer, made up with 10 ml of additional buffer and centrifuged as described [lacuna]. The pellet is then resuspended in buffer and diluted to give a homogenate which contains 60 mg of material/ml.  
0.1 ml of the suspension, 100 µl of a 5 nM solution of [<sup>3</sup>H]ketanserin, 100 µl of a solution of the test compound (concentration in the range from 10<sup>-5</sup> to 10<sup>-10</sup> mol per litre) are added to the incubation tubes and made up to 1 ml with buffer. The tubes are incubated for 15 minutes at 37°C. After termination of the incubation by immersing the tubes in an ice bath, the cooled suspension is filtered through a glass filter in vacuo. The filters are washed 3 × with 5 ml of cold buffer and then transferred to scintillation tubes. The filters are analysed by means of liquid scintillation spectrometry in 8 ml of Triton X scintillator fluid.

The test results of the 5-HT<sub>2A</sub> receptor binding test by some representative compounds of the formula I are compiled in Table A below. The IC<sub>50</sub> values are indicated for the binding tests.

Table A

IC<sub>50</sub> values (concentrations in mol/l at which 50% of the radioactive ligands are displaced from the binding sites) of representative compounds of the formula I.



I

A = CH<sub>3</sub> (if not stated otherwise)

10

R <sup>1</sup>	R <sup>2</sup>	Salt	Racemate (rac)/enan- tiomer (+) or (-)	M.p. [°C]	IC <sub>50</sub>
5-chloro- thiophen- 2-yl	4-fluoro- phenyl	HCl	rac	210-211	6.9E-10
5-chloro- thiophen- 2-yl	"	HCl	(+)	210-211	1.1E-09
thiophen- 2-yl	4-fluoro- phenyl	HCl	rac	222-223	6.0E-09
4-fluoro- phenyl	4-fluoro- phenyl	base	rac	122-123	1.3E-09
"	"	HCl	(-)	185-186	5.7E-08
"	"	HCl	(+)	187-188	3.5E-10
thiophen- 3-yl	4-fluoro- phenyl	base	rac	94-95	2.2E-09
"	"	HCl	(-)		2.5E-07
"	"	HCl	(+)		3.3E-09
5-chloro- thiophen- 2-yl*	"	HCl	rac	209-211	3.2E-08



2-methyl-thiazol-4-yl	"	base	rac	97-99	6.6E-08
5-chloro-thiophen-2-yl	2,4-difluorophenyl	HCl	rac	181-183	5.5E-09
4-fluorophenyl	"	HCl	rac	220-222	7.0E-10
"	"	HCl	(-)	212-214	2.2E-08
"	"	HCl	(+)	211-212	7.2E-10
5-methyl-thiophen-2-yl	4-fluorophenyl	base	rac	89	8.9E-10
2,4-dichlorophenyl	"	base	rac	102-103	2.0E-09
4-pyridyl	"		rac	77-78	2.2E-07
2,5-dichloro-thiophen-3-yl	"	HCl	rac	72.5	2.2E-09
2-chloro-3-methyl-thiophen-5-yl	"	HCl	rac	171-174	4.2E-09
5-bromo-thiophen-2-yl	"	HCl	rac	186-188	3.9E-09
2,4-difluorophenyl	"	HCl	rac	195-197	8.3E-10
"	"	HCl	(-)	202-204	4.0E-08
"	"	HCl	(+)	204-206	2.9E-09
2-chloro-5-methyl-thiophen-4-yl	"	HCl	rac	105	4.1E-09

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5-methoxy-thiophen-2-yl	"	HCl	rac	174-175	2.1E-08
4-tri-fluoro-methyl-phenyl	"	HCl, hyd-rate	rac	69-72	3.2E-08
5-chloro-thiophen-2-yl	4-tri-fluoro-methyl-phenyl	HCl	rac	196-198	8.6E-09
2-tolyl	"	HCl	rac	250-253	1.4E-09
4-cyano-phenyl	4-fluoro-phenyl	HCl	rac	227-228	2.7E-8
4-fluoro-phenyl	2,3-di-methoxy-phenyl	HI	rac	199-200	1.1E-08
5-chloro-thiophen-2-yl	phenyl	HI	rac	177-178	8.3E-10
4-fluoro-phenyl	phenyl	HI	rac	205-207	6.8E-10
4-fluoro-phenyl	5-chloro-thiophen-2-yl	base	rac	159-160	7.5E-10
5-chloro-thiophen-2-yl	4-chloro-phenyl	HCl	rac	192-193	2.6E-09
4-fluoro-phenyl	4-chloro-phenyl	HCl	rac	201-203	1.3E-09
4-fluoro-phenyl	benzo[1,4]-dioxan-5-yl	HCl	rac	209-212	3.7E-09
Comparison from EP 0531410					

4-fluoro-phenyl***	2,3-dimethoxy-phenyl				1-5E-10
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\* A = ethyl

\*\*\* A = H

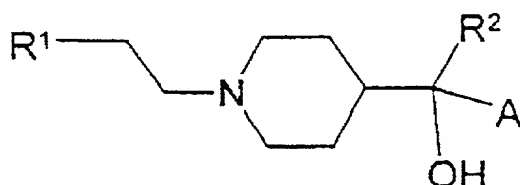
# Example A2

5

## Table B

Suppression of behaviour elicited (head-twitching in mice) by some representative compounds of the formula I (DOI antagonism)

10



I

A = CH<sub>3</sub> (if not stated otherwise)

15

R <sup>1</sup>	R <sup>2</sup>	Salt	Racemate (rac)/enantiomer (+) or (-)	M.p. [°C]	Inhibition [%]
5-chlorothiophen-2-yl	4-fluorophenyl	HCl	rac	210-211	
"	"	HCl	(+)	210-211	21
"	"	HCl	(-)	210-211	
4-fluorophenyl	2,4-difluorophenyl	HCl	(+)	211-212	
2,4-difluorophenyl	4-fluorophenyl	HCl	(+)	204-206	

4-fluoro-phenyl	phenyl	HI	rac	205-207	
4-fluoro-phenyl	5-chloro-thiophen-2-yl		rac	159-160	26
5-chloro-thiophen-2-yl	4-chloro-phenyl	HCl	rac	192-193	28
4-fluoro-phenyl	4-chloro-phenyl	HCl	rac	201-203	96
4-fluoro-phenyl	benzo[1,4]-dioxan-5-yl	HCl	rac	209-212	9
4-fluoro-phenyl	4-tri-fluoro-methyl-phenyl	HCl	rac	182-183	61
Comparison from EP 0531410:					
4-fluoro-phenyl***	2,3-di-methoxy-phenyl				0

\*\*\* A = H

On oral administration, the compounds according to the invention exhibit improved suppression of the behaviour induced by DOI. This indicates an unexpected improvement in the bioavailability in comparison with the prior art.

#### 10 Example B1

A solution of 0.88 g of 2-chloro-5-(2-chloro-ethyl)thiophene in 10 ml of acetonitrile is treated with 1.3 g of 1-(4-fluorophenyl)-1-piperidin-4-yl-ethanol, hydrochloride and 0.82 g of NaHCO<sub>3</sub> and stirred at 80° for 8 hours. After customary working-up, 1.3 g

of 1-{1-[2-(5-chlorothiophen-2-yl)ethyl]piperidin-4-yl}-1-(4-fluorophenyl)ethanol are obtained.

The residue is dissolved in acetone, treated with ether/HCl and the hydrochloride, m.p. 210-211°, is  
5 obtained after crystallization.

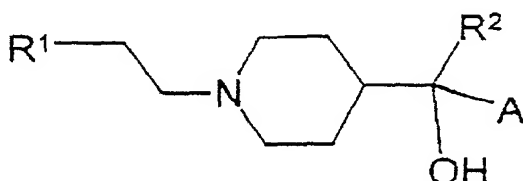
After separation of the racemate, the two enantiomers

(+)-1-{1-[2-(5-chlorothiophen-2-yl)ethyl]piperidin-  
10 4-yl}-1-(4-fluorophenyl)ethanol, hydrochloride,  
specific rotation in methanol: + 10.2° and  
(-)-1-{1-[2-(5-chlorothiophen-2-yl)ethyl]piperidin-  
4-yl}-1-(4-fluorophenyl)ethanol, hydrochloride, m.p.  
210-211, specific rotation in methanol: -10.6°  
15 are obtained.

The compounds below are obtained analogously

20 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-  
1-(4-fluorophenyl)ethanol, m.p. 122-123°,  
(+)-1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-  
1-(4-fluorophenyl)ethanol, hydrochloride, m.p.  
187-188°, specific rotation in methanol: + 10.3°;  
25 (-)-1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-1-(4-  
fluorophenyl)ethanol, hydrochloride, m.p. 185-186°,  
specific rotation in methanol: -10.6°;  
1-{1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl}-  
1-(4-fluorophenyl)ethanol, hydrochloride, m.p.  
30 222-223°;

and also the compounds of the formula I listed in Table  
1 below



I

A = CH<sub>3</sub>

(if not stated otherwise)

5 Table 1

R <sup>1</sup>	R <sup>2</sup>	Salt	Racemate (rac)/enan- tiomer (+) or (-)	Rotation in methanol [°]	M.p. [°C]
thiophen- 3-yl	4-fluoro- phenyl		rac		94-95
"	"	HCl	(-)	-12.0	
"	"	HCl	(+)	+11.1	
5-chloro- thiophen- 2-yl*	"	HCl	rac		209-211
5-chloro- thiophen- 2-yl**	"	base	rac		122-124
2-methyl- thiazol- 4-yl	"	base	rac		97-99
5-chloro- thiophen- 2-yl	2,4-di- fluoro- phenyl	HCl	rac		181-183
4-fluoro- phenyl	"	HCl	rac		220-222
"	"	HCl	(-)		212-214
"	"	HCl	(+)		211-212
5-methyl- thiophen- 2-yl	4-fluoro- phenyl	base	rac		89
4-methyl- thiazol-5- yl	"	oxalate, hydrate	rac		141-142

2,4-di-chloro-phenyl	"	base	rac		102-103
4-pyridyl	"	base	rac		77-78
2,5-di-chloro-thiophen-3-yl	"	HCl	rac		72.5
2-chloro-3-methyl-thiophen-5-yl	"	HCl	rac		171-174
5-bromo-thiophen-2-yl	"	HCl	rac		186-188
2,4-di-fluoro-phenyl	"	HCl	rac		195-197
"	"	HCl	(-)		202-204
"	"	HCl	(+)		204-206
2-chloro-5-methyl-thiophen-4-yl	"	HCl	rac		105
5-methoxy-thiophen-2-yl	"	HCl	rac		174-175
4-tri-fluoro-methyl-phenyl	"	HCl, hydrate	rac		69-72
5-chloro-thiophen-2-yl	4-tri-fluoro-methyl-phenyl	HCl	rac		196-198
4-fluoro-phenyl	"	HCl	rac		182-183

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2-fluoro-phenyl	4-fluoro-phenyl	HCl	rac		227-230
2-tri-fluoro-methyl-phenyl	"	HCl	rac		207-210
2-tolyl	"	HCl	rac		250-253
2,6-di-fluoro-phenyl	"	HCl	rac		194-197
3,4-di-fluoro-phenyl	"	HCl	rac		204-206
2,3-di-fluoro-phenyl	"	HCl	rac		245-246
3-fluoro-phenyl	"	HCl	rac		240-241
2-chloro-6-fluoro-phenyl	"	HCl	rac		192-195
2-fluoro-4-tri-fluoro-methyl-phenyl	"	HCl	rac		212-214
3-fluoro-5-tri-fluoro-methyl-phenyl	"	HCl	rac		227-229
4-fluoro-2-tri-fluoro-methyl-phenyl	"	HCl	rac		180

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3-fluoro- 4-tri- fluoro- methyl- phenyl	"	HCl	rac		181-183
2-fluoro- 6-tri- fluoro- methyl- phenyl	"	HCl	rac		199-201
2-fluoro- phenyl	2,4-di- fluoro- phenyl	HCl	rac		235-237
4-cyano- phenyl	4-fluoro- phenyl	HCl	rac		227-228

\* A = ethyl \*\* A = isopropyl

#### Example B2

5

100 mg of Mg are introduced into 5 ml of abs. diethyl ether in an apparatus flushed with nitrogen and a solution of 0.25 ml of methyl iodide in 5 ml of abs. ether is added dropwise with stirring. After 20 minutes, a solution of 0.75 g of {1-[2-(2,3-dimethoxyphenyl)ethyl]piperidin-4-yl}-(4-fluorophenyl)-methanone in 10 ml of THF is added dropwise. The mixture is subsequently stirred for one hour and after customary working-up 0.36 g of 1-{1-[2-(2,3-dimethoxyphenyl)ethyl]piperidin-4-yl}-1-(4-fluorophenyl)ethanol, hydroiodide, m.p. 199-200°, is obtained.

The compounds below are obtained analogously

20 1-{1-[2-(5-chlorothiophen-2-yl)ethyl]piperidin-4-yl}-1-phenylethanol, hydroiodide, m.p. 177-178°,  
1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-1-phenylethanol, hydroiodide, m.p. 205-207°,

1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-1-(5-chlorothiophen-2-yl)ethanol, m.p. 159-160°,

1-{1-[2-(5-chlorothiophen-2-yl)ethyl]piperidin-4-yl}-1-(4-chlorophenyl)ethanol, hydrochloride, m.p. 192-193°,

- 5 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-1-(4-chlorophenyl)ethanol, hydrochloride, m.p. 201-203°,  
1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-  
1-(benzo[1,4]dioxan-5-yl)ethanol, hydrochloride, m.p. 209-212°.

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The following examples relate to pharmaceutical preparations:

**Example A: Injection vials**

- 5 A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile-filtered, filled into injection vials, lyophilized and aseptically sealed.
- 10 Each injection vial contains 5 mg of active compound.

**Example B: Suppositories**

- 15 A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

**Example C: Solution**

- 20 A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of  $\text{NaH}_2\text{PO}_4 \times 2 \text{ H}_2\text{O}$ , 28.48 g of  $\text{NaH}_2\text{PO}_4 \times 12 \text{ H}_2\text{O}$  and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

**Example D: Ointment**

- 25 500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

**Example E: Tablets**

- 30 A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed in a customary manner to give tablets such that each
- 35 tablet contains 10 mg of active compound.

**Example F: Coated tablets**

Analogously to Example E, tablets are pressed and are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colourant.

5

**Example G: Capsules**

2 kg of active compound of the formula I are filled into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

10

**Example H: Ampoules**

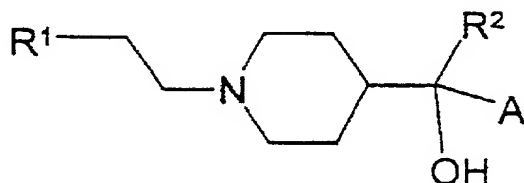
A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is filled into ampoules, lyophilized under aseptic conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

15

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## Patent Claims

1. Compounds of the formula I



in which

$R^1, R^2$  in each case independently of one another are aryl or Het,

aryl is phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, CN, A, OA or OH,

Het is a mono- or binuclear unsaturated heterocyclic ring system which is unsubstituted or mono-, di- or trisubstituted by Hal, A, CN, OA or OH and which contains one, two or three identical or different heteroatoms such as nitrogen, oxygen and sulfur,

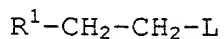
A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

and their physiologically acceptable salts and solvates.

2. Process for the preparation of compounds of the formula I according to Claim 1, characterized in that

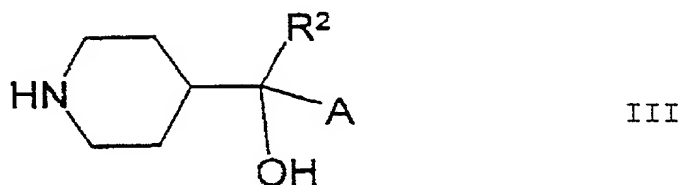
a) a compound of the formula II



II

in which L is Cl, Br, I or a free or reactively  
[sic] functionally modified OH group,  
and R<sup>1</sup> has the meaning indicated in Claim 1,  
is reacted with a compound of the formula III

5

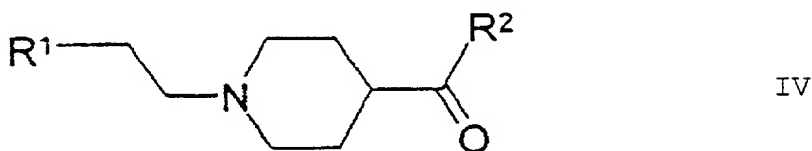


in which R<sup>2</sup> and A have the meanings indicated in  
Claim 1,

10

or

b) a compound of the formula IV

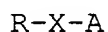


15

in which R<sup>1</sup> and R<sup>2</sup> have the meanings indicated in  
Claim 1,

is reacted with a compound of the formula V

20



V

in which R is iodine or bromine, X is Mg  
and A has the meaning indicated in Claim 1,  
in a Grignard reaction,

25

or

c) it is liberated from one of its functional  
derivatives by treating with a solvolysing or  
hydrogenolysing agent,

30

or

5 d) a base of the formula I which is obtained is converted into one of its salts by treating with an acid.

10 3. Compounds of the formula I according to Claim 1, and their physiologically acceptable salts and solvates as medicaments.

15 4. Compounds of the formula I according to Claim 1, and their physiologically acceptable salts and solvates as medicaments having 5-HT<sub>2A</sub> receptor-antagonistic action.

20 5. Medicament according to Claim 4 for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, anorexia nervosa, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

30 6. Pharmaceutical preparation, comprising at least one medicament according to Claim 5 and also, if appropriate vehicles and/or excipients and, if appropriate, other active compounds.

35 7. Use of compounds according to Claim 1 and/or of their physiologically acceptable salts and solvates for the production of a medicament having 5-HT<sub>2A</sub> receptor-antagonistic action.

8. Use according to Claim 7 for the production of a medicament for the treatment of psychoses, schizophrenia, depression, neurological disorders,

5 memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, anorexia nervosa, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

SECRET



(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES  
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FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI-Patent  
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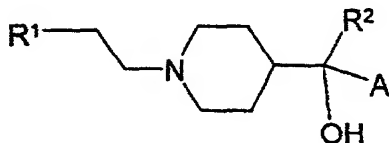
Veröffentlicht:

- Mit internationalem Recherchenbericht.
- Vor Ablauf der für Änderungen der Ansprüche geltenden  
Frist; Veröffentlichung wird wiederholt, falls Änderungen  
eintreffen.

Zur Erklärung der Zweibuchstaben-Codes, und der anderen  
Abkürzungen wird auf die Erklärungen ("Guidance Notes on  
Codes and Abbreviations") am Anfang jeder regulären Ausgabe  
der PCT-Gazette verwiesen.

(54) Title: PIPERIDINE ALCOHOLS

(54) Bezeichnung: PIPERIDINALKOHOLE



(1)

disorders, (OCD).

(57) Zusammenfassung: Verbindungen der Formel (I), worin R<sup>1</sup>, R<sup>2</sup> und A die in Anspruch 1 angegebenen Bedeutungen besit-  
zen, sind potente 5-HT<sub>2A</sub>-Antagonisten und eignen sich zur Behandlung von Psychosen, Schizophrenie, Depression, neurologi-  
schen Störungen, Gedächtnisstörungen, Morbus Parkinson, amyotropher Lateralsklerose, der Alzheimer Krankheit, der Huntington  
Krankheit, Essstörungen wie Bulimie, nervöser Anorexie, des prämenstrualen Syndroms und/oder zur positiven Beeinflussung von  
Zwangsverhalten (obsessive-compulsive disorder, OCD).

(57) Abstract: The invention relates to compounds of formula  
(I), wherein R<sup>1</sup>, R<sup>2</sup> and A have the meanings given in claim 1,  
are potent 5-HT<sub>2A</sub> antagonists and are suitable for treating psy-  
choses, schizophrenia, depression, neurological disorders, im-  
paired memory, Parkinson's disease, amyotrophic lateral scler-  
osis, Alzheimer's disease, Huntington's disease, eating disor-  
ders such as bulimia and anorexia nervosa, Pre-Menstrual Syn-  
drome and/or for positively influencing obsessive-compulsive

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Docket No.  
Merck

## Declaration and Power of Attorney For Patent Application English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Piperidine alcohols

the specification of which

(check one)

- ☐ is attached hereto.  
☒ was filed on 08.08.2000 as United States Application No. or PCT International Application Number PCT/EP00/07664 and was amended on \_\_\_\_\_ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

199 39 756.2      Germany      21.08.1999  
(Number)      (Country)      (Day/Month/Year Filed)

☐

\_\_\_\_\_  
(Number)      (Country)      (Day/Month/Year Filed)

☐

\_\_\_\_\_  
(Number)      (Country)      (Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Residence	
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